UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,037	07/23/2003	Warren J. Scherer	512-160	1255

7590 02/03/2010

Ronald J. Baron, Esq.
HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
02/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,037	SCHERER, WARREN J.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,12 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12 and 36* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 11-12 and 36 are presented for examination.

Applicant's Amendment filed November 18, 2009 has been received and entered into the instant application.

Claims 11-12 and 36 are pending and under examination. Claims 11-12 and 36 are amended.

Applicant's arguments, filed November 18, 2009, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and objections are either reiterated or newly applied. They constitute the complete set of rejections and objections presently being applied to the instant application.

Objection to the Claims (New Grounds of Objection)

Claim 12 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 11. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement, New Matter (New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-12 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention.

Present claim 36 is directed to a method of treating facial flushing associated with menopause-associated hot flashes in a human in need thereof, the method comprising topically administering a composition comprising an effective amount of a single component to reduce cutaneous facial flushing, wherein the single component consists of brimonidine or brimonidine tartrate, or combinations thereof, and a dermatologically acceptable carrier locally to facial skin of the human, wherein the single component acts locally to reduce cutaneous facial flushing.

In particular, the specification and claims as originally filed fail to provide adequate written description for the newly claimed limitation directed to the use of brimonidine *per se* or combinations of brimonidine and brimonidine tartrate (claim 36).

Relevant disclosure regarding this limitation identified above was found at, e.g., p.5, l.9-15, which states, "Selective α_2 adrenergic receptor agonists suitable for use in the subject invention include, and are not limited to, guanabenz, guanfacine, alpha-methyl DOPA (methydopamine), amphetamine, methylphenidate, lofexidine, moxonidine, dexmedetomidine, mivazerol, (2-imidazolin-2-ylamino) quinoxaline derivatives (including, but not limited to, brimonidine tartrate). Brimonidine tartrate is a quinoxaline derivative and quinoxaline derivatives having α_2 receptor agonist activity were originally suggested as therapeutic agents by U.S. Patent No. 4,029,792 which is hereby incorporated by reference in its entirety."

While such teachings have been fully and carefully considered, it is noted that such disclosure fails to be supportive of the concept of the use of brimonidine *per se* or combinations of both brimonidine and brimonidine tartrate. The disclosure of the use of, specifically, (2-imidazolin-2-ylamino)-quinoxaline derivative compounds, wherein the compound brimonidine tartrate is explicitly described, fails to provide adequate written support to now claim that the alpha-2 adrenergic receptor agonist is either brimonidine *per se* (i.e., not in a so-called "derivative" or tartrate salt form) or a combination of brimonidine *per se*

and brimonidine tartrate. This is a broadening of the subject matter both claimed and disclosed in the specification and claims as originally filed that is not adequately supported, either explicitly or implicitly, by the original disclosure. It is clear from what is disclosed in the originally filed specification and claims that Applicant was not in possession of the concept of the use of either brimonidine *per se* or a combination of brimonidine *per se* and brimonidine tartrate as the active agents used to reduce cutaneous facial flushing, since both the claims and disclosure as originally filed fail are specifically directed to the use of a (2-imidazolin-2-ylamino)-quinoxaline derivative compound, in particular, brimonidine tartrate, as the alpha-2 adrenergic agonist to be employed in the disclosed method of treatment.

As stated in MPEP §2163, "The subject matter of the claim need not be described literally (i.e., using the same terms of *in haec verba*) in order for the disclosure to satisfy the description requirement." However, considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the concept of administering brimonidine *per se* or a combination of brimonidine *per se* and brimonidine tartrate (claim 36).

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-12 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold et al. (WO 02/36144; May 2002) in view of Gil et al. (U.S. Patent Application Publication No. 2003/0229088;

Issued December 2003, Filed May 2002), Wymenga et al. ("Management of Hot Flushes in Breast Cancer Patients", *Acta Oncologia*, 41(3); 2002:269-275) and Ito (EP 10069124 A1; 2001), each already of record.

Arnold et al. teaches a medicament comprising one of more GnRH analogue compounds, optionally in combination with an estrogen or progestin compound, which may also be formulated in combination with at least one compound selected from, *inter alia*, alpha-adrenergic agonists (p.12, l.20-31). Arnold et al. further teaches that said medicament is useful for the treatment of side effects of ovarectomy or symptoms associated with reproductive senescence in female mammals (i.e., menopause; p.9, l.25-30), in particular, women (p.11, l.9-14), wherein such symptoms include vasomotor symptoms, especially hot flushes (p.10, l.10-14), and may be prepared in the form of creams or foams (p.15, l.6-12).

Though it is acknowledged that the therapy of Arnold et al. is a combination of at least two agents (i.e., a GnRH analogue compound with at least one compound selected from, *inter alia*, alpha-adrenergic agonists), such a teaching still meets Applicant's instant claims because the composition, as a whole, remains open to the inclusion of additional, unrecited elements as evidenced by the use of the transitional phrase "comprising" (see l.3 of instant claim 36). The description of the instantly claimed composition as 'comprising' an effective amount of a single component that 'consists' of brimonidine or brimonidine tartrate or combinations thereof does not limit the composition solely to this "single component" (i.e., brimonidine or its tartrate salt or even combinations thereof) because the overall composition is ultimately defined as being open to other elements via the phrase "comprising". Though Applicant appears to believe that the use of the phrase "consists of brimonidine" etc. limits the composition to only this single component, Applicant is reminded that the composition as a whole is defined as comprising this particular element and, therefore, very clearly permits the inclusion of other elements that are not specifically recited in the claim such as, in the instant case, the elements described by Arnold et al. See MPEP §2111.03[R-3].

Arnold et al. fails to teach (1) the use of brimonidine or brimonidine tartrate as the alpha-adrenergic agonist (claim 36); (2) topical administration of the composition locally to the facial skin (claim 36); or (3) the concomitant use of an additional agent as provided for in instant claims 11-12.

Gil et al. teaches known alpha-adrenergic agonists, including clonidine, brimonidine, tizanidine, etc. (p.1, para.[0009]) and salts thereof, including the tartrate salt (p.13, para.[0091]), and compositions thereof (p.13, para.[0096]) in dermatologically acceptable formulations, such as, e.g., a dermal patch, topical drops, creams, gels, or ointments, etc. (p.14, para.[0099]).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ the alpha-adrenergic agonist brimonidine or a salt thereof (such as, e.g., the tartrate salt of brimonidine) in the medicament disclosed by Arnold et al. as effective for the treatment of hot flashes that result from reproductive senescence in women because Gil et al. teaches that brimonidine (or its tartrate salt, for example) is one of a finite number of alpha-adrenergic agonists known in the prior art at the time of the invention to predictably function as agonists of alpha-adrenoreceptors. In other words, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ any one of the known alpha-adrenergic agonists (which, as evidenced by Gil et al., included brimonidine or brimonidine tartrate) into this formulation of Arnold et al. with a reasonable expectation of success because (1) a person with ordinary skill in the art has good reason to pursue known options within his or her technical grasp and (2) Arnold et al. teaches the desirability of including such an alpha-adrenergic agonist into the disclosed GnRH analogue formulation for the treatment of hot flashes that result from reproductive senescence in women.

Wymenga et al. teaches that menopausal flushing onset is abrupt and typically starts with a feeling of heat in the upper body that is generally associated with a visible reddening of the face (col.1, para.4, p.270). Wymenga et al. further teaches that administration of vitamin E (i.e., an antioxidant; see instant claims 11-12) in an amount of 800 I.U. per day to patients experiencing hot flushes demonstrated a

significant reduction in flushing, which, though on average was only a reduction in one flushing incident per day, was still suggested for use in treating hot flushes due to its non-toxic and inexpensive properties, as well as the fact that it is widely available (col.2, para.2, p.272).

Ito teaches compounds and pharmaceutical compositions containing said compounds in an effective amount and a pharmaceutically acceptable carrier (p.5, para.[0026]), and are useful for the treatment of disorders or medical conditions, such as inflammatory diseases (p.2, para.[0001]), wherein the condition to be treated is, *inter alia*, vasomotor disturbances including hot flushes (p.5, para.[0027]). Ito teaches that the compounds may be administered via topical administration for treatment of the disclosed diseases (p.14, para.[0071]) and should be administered topically when treating inflammatory conditions of the skin, preferably by way of creams, gels, pastes, ointments, etc. (p.14, para.[0076]).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to apply the cream or foam formulation of Arnold et al. topically to the site of the facial flushing in a patient experiencing menopausal-related hot flashes because (1) menopause-associated hot flashes result in visible reddening of the face, as evidenced by Wymenga et al., (2) treatment of diseases including hot flushes, as well as inflammatory conditions of the skin, should be treated topically, as evidenced by Ito, and (3) the skilled artisan would have recognized the advantage to directly treating the area of flushing with a topical formulation effective to treat such flushing by applying it directly to the affected area of skin, such as, e.g., directly to the face to treat facial flushing resulting from menopausal hot flashes, absent factual evidence to the contrary. Such a person would have been motivated to do so in order to treat the affected area while minimizing exposure of unaffected areas to the pharmacologic formulation.

Furthermore, one of skill in the art would have also found it *prima facie* obvious to combine the formulation of Arnold et al. in view of Gil et al. with the vitamin E compound in light of the disclosure of Wymenga et al. because Wymenga et al. teaches the activity of vitamin E in effecting a significant

reduction in the incidence of menopausal hot flushes and, thus, the cutaneous flushing associated therewith. Motivation to administer both compounds/compositions together flows logically from the very fact that each discrete agent was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two agents, when combined, would have, at minimum, additive, if not synergistic, effects in reducing the incidence of menopausal hot flushes (and the cutaneous flushing that results from the same) when combined.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that the Examiner relies on Gil for teaching topical administration of alpha-adrenoreceptor agonists such as brimonidine, but opines that Gil relates exclusively to the treatment of pain, which is unrelated to hot flushes. Still further, Applicant alleges that the Examiner has misinterpreted Ito because the "only embodiment for which Ito teaches topical administration is 'when treating inflammatory conditions of the skin'" (p.5, Remarks) and insists that, because Ito does not state that hot flushes are inflammatory conditions of the skin, the reference does not disclose topical treatment of hot flushes. Applicant further asserts that the composition of Ito is completely unrelated to alpha-adrenoreceptor agonists because the mechanism by which the composition functions is by agonizing ORL-1 receptors, which is not the same as that instantly claimed, and, thus, fails to suggest treating hot flushes topically. Lastly, Applicant opines that the only alpha-adrenoreceptor agonists mentioned in Arnold are phenylpropanolamine and phenylephrine, which are employed for

different uses in the art than that claimed and, therefore, Arnold fails to "even hint at treating hot flushes with alpha-adrenoreceptor agonists" (p.5, Remarks).

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Firstly, Applicant states that the Examiner has relied on Gil for teaching topical administration of brimonidine, but opines that Gil relates exclusively to the treatment of pain, which is unrelated to hot flushes. This is unpersuasive. Gil was relied upon solely for the teachings of (1) known alpha-adrenergic agonists, including clonidine, brimonidine, tezanidine, etc. (p.1, para.[0009]) and salts thereof, including the tartrate salt (p.13, para.[0091]) and (2) that such agonists were known to be amenable to formulation in dermatologically acceptable compositions thereof (p.13, para.[0096]) in the form of, e.g., a dermal patch, topical drops, creams, gels or ointments, etc. (p.14, para.[0099]). Gil was not *per se* relied upon for suggesting the topical administration of brimonidine, but rather the amenability of brimonidine to be formulated into a composition for topical application. Nevertheless, it is immaterial that the disclosure of Gil as a whole is directed to the treatment of pain. The primary reference to Arnold et al. clearly provides for the use of a GnRH analogue compound in combination with, *inter alia*, at least one alpha-adrenergic agonist (p.12, l.20-31) for the treatment of vasomotor symptoms associated with menopause, including hot flushes (p.9, l.25-30; p.10, l.10-14; p.11, l.9-14). Though Arnold et al. does not specifically disclose brimonidine or brimonidine tartrate as the specific alpha-adrenergic agonist to be used, the very teaching of an alpha-adrenergic agonist *per se* indicates that any one or more of such agonists may be employed to achieve this therapeutic effect as disclosed in Arnold et al.

Applicant's argument that, because Gil teaches methods of treating pain using alpha-adrenergic agonists, the reference is not relevant to the instant claims is unimpressive. Gil was relied upon for its teaching of other functionally equivalent alpha-adrenergic agonist compounds that were known in the art at the time of the invention and would have reasonably been employed in the method taught and/or suggested by Arnold et al. for the treatment of hot flushes. The fact that Gil et al. discloses the use of such

alpha-adrenergic agonists for alleviating pain does not negate the teaching that brimonidine is a compound that functions as an alpha-adrenergic agonist and that this fact was well established in the art at the time of the invention. Applicant is reminded that the test for obviousness is not whether the features of a secondary reference (i.e., in this case, Gil et al.) may be bodily incorporated into the structure of the primary reference (i.e., in this case, Arnold et al.), nor that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, it is clear that the teachings of Arnold et al. (i.e., the use of a combination therapy comprising at least one alpha-adrenergic agonist for the treatment of vasomotor symptoms, such as hot flushes, in menopausal women) coupled with those of Gil et al. (i.e., that brimonidine and its tartrate salt were known alpha-adrenergic agonists at the time of the invention) clearly provide a suggestion to employ brimonidine or its tartrate salt as the alpha-adrenergic agonist of the therapy disclosed by Arnold et al, absent factual evidence to the contrary.

Secondly, Applicant argues two points against the cited reference to Ito: (1) that Ito only discloses topical administration for the treatment of inflammatory conditions of the skin and fails to teach hot flushes as an inflammatory skin condition and (2) that the composition of Ito functions by agonizing ORL-1 receptors, which is a completely unrelated mechanism to that of the instant claims, and, therefore, fails to suggest topical treatment of hot flushes. Each of these points raised by Applicant is unpersuasive. Though it is acknowledged that Ito discloses the use of topical administration preferably for the treatment of inflammatory skin conditions, the fact remains that Ito clearly discloses the use of topical administration for the treatment of any of the diseases taught therein (see, e.g., p.14, para.[0071]). In other words, Ito does not restrict his teaching of topical administration solely for the purpose of treating inflammatory conditions of the skin. That being said, it is asserted that hot flushes would still be understood to fall within this teaching of inflammatory conditions of the skin because, during a hot flash,

the blood vessels near the skin surface dilate, thereby increasing blood flow, which, in turn, causes the skin to become warm and flushed. This is clearly an inflammatory reaction and, thus, is understood to be considered an inflammatory condition of the skin. However, even if, *arguendo*, hot flushes were not considered to be an inflammatory condition of the skin (which the Examiner does not necessarily concede), Ito clearly teaches topical administration as a means of administration for treating any of the disclosed conditions, *inter alia*, hot flushes and, as a result, one of skill in the art at the time of the invention would have understood that hot flushes would have been amenable to topical treatment using effective pharmaceutical therapies, such as the formulation described by Arnold et al. taken in view of Gil et al.

Next, Applicant's argument that Ito fails to suggest topical administration of hot flushes because the mechanism by which the composition of Ito functions and that of the instant claims is different is unpersuasive. Ito was cited for its teaching that conditions such as hot flushes are amenable to, specifically, topical treatment of an effective therapeutic formulation. The fact that the actual formulation employed by Ito functions via a mechanism of action that differs from Applicant's instantly claimed invention is immaterial to the instant finding of obviousness. Applicant's urging that such a teaching renders the reference inapplicable to the instant case appears to based on Applicant's desire to bodily incorporate the teachings of Ito into the primary reference(s) in order to allege that it is not pertinent. As stated *supra*, the attempt to bodily incorporate the teachings of a secondary reference into the structure of the primary reference is unpersuasive and is not the test for obviousness. Here, the fact that Ito achieves treatment of hot flushes via administering a composition with a different mechanism of action is peripheral to the fact that Ito provides a clear teaching and/or suggestion to employ, in particular, topical administration of an active pharmaceutical formulation for the treatment of hot flushes. This coupled with the teachings of Arnold et al. in view of Gil et al. further provides a clear basis to apply the suggested formulation in a topical manner to the afflicted patient. Applicant is again reminded that the test for

obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference, nor that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Thirdly, and lastly, Applicant opines that the only alpha-adrenoreceptor agonists mentioned in Arnold et al. are phenylpropanolamine and phenylephrine, which are employed for different uses in the art than that claimed and, therefore, Arnold et al. fails to "even hint at treating hot flushes with alpha-adrenoreceptor agonists" (p.5, Remarks). This argument is both perplexing and unpersuasive. Though it is acknowledged that Arnold et al. discloses phenylpropanolamine and phenylephrine as two alpha-adrenergic receptor agonists that may be used (see, e.g., p.14, l.1-2 of Arnold et al.), it is urged that these two agonists are disclosed as exemplary species of the genus as clearly evidenced by the use of "e.g." in the disclosed list. Thus, it is clear that Arnold et al. did not intend to limit such a disclosure of alpha-adrenergic receptor agonists to only those two species disclosed in the description of the invention (i.e., phenylpropanolamine and phenylephrine). In fact, it is maintained that the clear suggestion provided by Arnold et al. to couple the GnRH analogue compound with a second active agent, such as, *inter alia*, an alpha-adrenergic agonist is a clear teaching that any one such compound that is known to function as an alpha-adrenergic agonist may be employed in the disclosed therapeutic formulation, absent factual evidence to the contrary. Thus, Applicant's argument that somehow Arnold et al. is restricted to the use of phenylpropanolamine and phenylephrine and fails to suggest the use of any other alpha-adrenergic agonists outside of these two compounds is clearly without merit.

Finally, Applicant's statement that Arnold fails to "even hint at treating hot flushes with alpha-adrenoreceptor agonists" (p.5, Remarks) clearly fails to fully appreciate the teachings of the reference. Arnold et al. explicitly teaches a medicament comprising one or more GnRH analogue compounds,

optionally in combination with an estrogen or progestin compound, which may also be formulated in combination with at least one compound selected from, *inter alia*, alpha-adrenergic agonists (p.12, l.20-31) and further teaches that said medicament is useful for the treatment of side effects of ovarectomy or symptoms associated with reproductive senescence in female mammals (i.e., menopause; p.9, l.25-30), in particular, women (p.11, l.9-14), wherein such symptoms include vasomotor symptoms, especially hot flushes (p.10, l.10-14), and may be prepared in the form of creams or foams (p.15, l.6-12). In view of these teachings, it is explicitly clear that Arnold et al. provides not only a teaching, but a clear suggestion, to employ a composition comprising an alpha-adrenergic agonist for the treatment of vasomotor symptoms associated with menopause, including hot flushes, in women. Applicant's allegation to the contrary is not factually supported by the teachings of the reference and is, as a result, unpersuasive in establishing nonobviousness of the instantly claimed invention.

For these reasons *supra*, rejection of claims 11-12 and 36 is proper.

Conclusion

Rejection of claims 11-12 and 36 is proper.

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the

mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

January 20, 2010

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614